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EXAMINER

FETTEROLF, BRANDON J

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 06/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/748,003

Applicant(s)

EGILMEZ, NEJAT K.

Examiner

Brandon J. Fetterolf, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 March 2006.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
4a) Of the above claim(s) 12-26 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-11 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 03/20/2006 in response to the previous Non-Final Office Action (12/30/2005) is acknowledged and has been entered.

Claims 1-26 are currently pending.

Claims 12-26 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-11 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

New Rejections necessitated by amendments:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting growth of gastrointestinal tumors comprising the steps of orally administering to an individual with one or more gastrointestinal tumors, a formulation comprising: a) polymeric microspheres encapsulating a drug composition comprising sulindac and polymeric microspheres encapsulating a drug composition comprising IL-12; or b) a polymeric microsphere encapsulating a drug composition comprising sulindac and IL-12; wherein said oral administration of the encapsulated sulindac and IL-12 is synergistically effective in inhibiting the growth of one or more gastrointestinal tumors which each alone is individually incapable of

achieving (Webster's definition of synergism), does not reasonably provide enablement for a method of inhibiting growth of gastrointestinal tumors comprising the steps of orally administering to an individual with one or more gastrointestinal tumors, a formulation comprising : a) polymeric microspheres encapsulating a drug composition comprising sulindac and polymeric microspheres encapsulating a drug composition comprising IL-12; or b) a polymeric microsphere encapsulating a drug composition comprising sulindac and IL-12; wherein said oral administration of the encapsulated sulindac and IL-12 is synergistically effective in inhibiting the growth of one or more gastrointestinal tumors such that the combined action of each agent is greater than the sum of each acting separately (Stedman's dictionary of synergism see attached). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large

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quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In *Wands*, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (*Wands*, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of *Wands* factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of inhibiting growth of gastrointestinal tumors comprising the steps of orally administering to an individual with one or more gastrointestinal tumors, a formulation comprising: a) polymeric microspheres encapsulating a drug composition comprising sulindac and polymeric microspheres encapsulating a drug composition comprising IL-12; or b) a polymeric microsphere encapsulating a drug composition comprising sulindac and IL-12; wherein said oral administration of the encapsulated sulindac and IL-12 is synergistically effective in inhibiting the growth of one or more gastrointestinal tumors. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of inhibiting growth of gastrointestinal tumors comprising the steps of orally administering to an individual with one or more gastrointestinal tumors, a formulation comprising: a) polymeric microspheres encapsulating a drug composition comprising sulindac and polymeric microspheres encapsulating a drug composition comprising IL-

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12; or b) a polymeric microsphere encapsulating a drug composition comprising sulindac and IL-12; wherein said oral administration of the encapsulated sulindac and IL-12 is synergistically effective in inhibiting the growth of one or more gastrointestinal tumors.

Guidance in the specification and Working Examples

The specification teaches that oral administration of polymeric encapsulated (herein referred to as PLA-PIL) sulindac or PLA-PIL- IL 12 promotes the regression of established intestinal adenomas in adult APC/Min ^{+/+} mice (page 18, Example 11 and Figure 11). Moreover, the specification teaches that the combined administration of sulindac and IL-12-encapsulated PLA-PIN microspheres shows a synergistic effect in inducing the regression of established tumors (page 19, lines 2-5, Figure 11). Thus, while the specification teaches that the co-administration of sulindac and IL-12 encapsulated microspheres shows a synergistic effect in reducing the regression of established tumor as defined by Webster's dictionary, e.g., the action of two or more substances to achieve an effect which each is incapable of achieving on its own, the specification does not appear to reasonably convey a synergistic effect in reducing the regression of established tumor as defined by Stedman's dictionary, e.g., coordinated or correlated action of two or more structures, agents, or physiologic processes so that the combined action is greater than the sum of each acting separately.

Quantity of experimentation

The quantity of experimentation in the areas of predicting synergism of two agents for cancer therapy is extremely large given the unpredictability associated with accurately determining whether the action of two agents in combination is synergistic or merely additive.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that there are several different definitions of synergism, as evidenced by the Webster Dictionary and Stedman's Medical Dictionary discussed above, and that the choice of the definition is a matter of personal preference. Moreover, the state of the art at the time of filing was such that one of skill could recognize that IL-12 or sulindac have individually been taught in the prior art for treating gastrointestinal tumor (Mathiowitz et al. of record in the prior office action and Giardiello et al. of

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record in the prior office action). Furthermore, the state of the art at the time of the filing was such that one of skill could recognize that bioadhesive polymeric microcapsules containing drugs or other bioactive substances serve as therapeutics for the treatment of diseases associated with the gastrointestinal tract, wherein drug delivery via the mucosal membranes provides greater drug bioavailability (Mathowitz, 2001 of record, column 2, paragraph 0015). In addition, those of skill in the art at the time of filing could recognize that specific inhibition of cyclooxygenase 2 (COX-2) restores antitumor reactivity by altering the balance of IL-10 and IL-12 synthesis (Stolina et al. J. Immunology 2000; 164: 361-370). Specifically, Stolina et al. teach that COX-2 inhibition results in the up-regulation of IL-12, which has been shown to be down-regulated in tumor bearing mice, and administration of IL-12 has been shown to have antitumor effects (page 368, 1st column, last paragraph). However, the prior art appears to be silent on a synergistic effect, as defined by Stedman's dictionary, on the inhibition of tumor growth resulting from the co-administration of sulindac and IL-12, let alone co administration of any COX-2 inhibitor, which sulindac is, and IL-12.

In the instant case, those of skill in the art would recognize the unpredictability that the combination of two anti-cancer agents would display a synergistic relationship on tumors. For example, Wiesenthal (<http://weisenthal.org/feedback.html>, 2/04/2002) discusses the question of synergy between drug combinations and diseases. In particular, Wiesenthal states that "true synergy is rather uncommon in most adult tumors, wherein most drug combinations in disease such as lung cancer, breast cancer, and ovarian cancer are merely additive (whole equals the sum of its parts) and not synergistic." Further, Tallarida (Drug Synergism and Dose-effect Analysis, Chapman & Hall/CRC, Boca Raton, 2000, pp. 1-13) and Berenbaum ("Synergy, additivism and antagonism in immunosuppression," Clin exp Immunol 28:1-18, 1977) disclose that to demonstrate the synergistic effect of two treatment agents, one must first prepare a dose-response curve for each agent alone (see Fig. 1 of Berenbaum). One must also prepare a number of combination treatments containing varying amounts of each agent. The results of all the treatments, each agent alone and the various combinations must be compared and analyzed quantitatively and statistically. The discussion on p. 2 of Berenbaum describes how the value obtained by measuring a response achieved by administering two pharmaceutical treatment agents is often mistaken for synergy when in reality it is the same as the effect obtained by using either agent alone. That is, the effect produced by administering agent A in a particular amount (e.g., x mg) and agent B in a particular amount (e.g., y mg) is the same as

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the one obtained by administering that total amount of agent A ($x + y$ mg). Berenbaum also provides an algebraic method and a geometric method for determining the nature of the interaction of two agents (see pp. 3-5). To produce a graph such as Fig. 2 (p. 5), a particular response (effect) must be achieved by administering each agent alone. Different doses of agent A and different doses of agent B create the axes. A line is drawn between the two intercepts (the additivism line). A number of combinations of agent A and agent B, containing varying amounts of A and varying amounts of B, are tested, and the response is measured. The combinations producing the response achieved in the amount equal to that of the intercept points are determined and plotted as data points on the graph. If these data points fall below the additive line, the effect of the combination is considered to be synergistic. If the data points fall above the additivism line, the effect is considered to be antagonistic. Tallarida discloses a similar analysis (see pp. 5-9).

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for defining what synergy means, and the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathiowitz et al. (US 2001/0043914, 2001) and Giardiello et al. (Gut, 1996; 38; 578-581) in view of Mathiowitz et al. (6,235,313, 2001).

Mathowitz et al. ('914) teach a method of treating a tumor comprising administering to an individual a formulation comprising a polymeric microsphere containing IL-12, wherein the

administration of the formulation is effective to treat said tumor (abstract). With regards to the polymeric microsphere, the '914 publication teaches that polymeric microsphere refers to polymeric particles including, but not limited to, polyanhydrides such as poly(lactide-co-glycolide), polycaprolactone, poly(fumaric-co-sebacic)acid and polyacrylic acid (page 5, paragraph 0047 to 0049 and page 12, paragraph 0105). With regards to the tumor, Mathowitz et al. teach that the tumors include, but are not limited to, colon and rectum cancer, and esophageal cancer (page 4, paragraph 0043). With regards to the polymeric microsphere, Mathowitz et al teach that the polymeric microspheres can be prepared by a phase inversion nanoencapsulation method (page 6, paragraph 0057). In addition, the '914 publication teaches a method of inhibiting tumor growth comprising administering a microparticle preparation containing IL-12 during a chemotherapeutic procedure, such as agents which function to inhibit a cellular activity which the cancer cell is dependent upon for continued survival (page 16, 2nd column, claims 32 and 34 of the PGPub and page 8, paragraph 0075) further teaches that the concentration of the IL-12 microspheres may be at a dose of about 0.2-70 micrograms for an adult of 70Kg body weight or at a dose of 3.5-21 micrograms (page 11, paragraph 0092).

Giardiello et al. teach a method of inhibiting the growth of colorectal adenomas comprising the steps of orally administering sulindac to an individual with a gastrointestinal tumor in an amount effective to inhibit the growth of the tumor (Abstract). With regards to the effective amount, the reference teaches that 150 mg of sulindac was given per dose (Abstract, *Results*).

Neither Mathowitz et al. ('914) or Giardiello et al. teach the combination of IL-12 and sulindac for the treatment of gastrointestinal tumors. Moreover, Mathowitz et al. do not explicitly teach that the formulation comprising a polymeric microsphere containing IL-12 is administered orally or that the polymeric microspheres are prepared by hot melt method. Giardiello et al. does not explicitly teach that sulindac is encapsulated in a polymeric microsphere or any of the properties recited therein.

Mathowitz et al. ('313) teach bioadhesive microspheres for use in drug delivery systems, wherein the microspheres can be composed of bioerodible polymers such as polyanhydrides, poly[lactide-co-glycolide] and polyorthoesters (column 7, lines 22-23). With regards to the microspheres, the patent teaches that the microspheres can be fabricated from different polymers using a variety of different methods including, but not limited to, hot melt microencapsulation

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(column 11, line 55 to column 12, line 55). Mathowitz et al. further disclose that the agents may be administered orally, wherein oral administration is advantageous with respect to both cost considerations as well as patient compliance and comfort (column 3, lines 50-57). Mathowitz et al. further teach that the bioadhesive molecules provide a drug delivery formulation that is useful for drug delivery via the mucosal membranes providing greater drug bioavailability (column 3, lines 50-60).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the polymeric microsphere containing IL-12 as taught by Mathowitz et al. ('914) and sulindac as taught by Giardiello et al. because each of the therapeutics had been individually taught in the prior art to be successful at treating gastrointestinal cancer. As such, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. In addition, one would have been motivated to do so because Mathowitz et al. ('914) already teaches the combination of IL-12 with another agent which functions to inhibit a cellular activity which the cancer cell is dependent upon for continued survival. Thus, one of ordinary skill in the art would have reasonable expectation of success that by administering a composition comprising IL-12 and sulindac, one would achieve an effective treatment of gastrointestinal tumors. Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to encapsulate the orally administered sulindac as taught by Giardiello et al. in a polymeric microsphere; and further, to administer the encapsulated IL-12 as taught by Mathowitz et al. ('914) and sulindac orally in view of Mathowitz et al. ('313) teachings that oral administration of polymeric microspheres provide greater drug bioavailability via the mucosal membranes and offers advantages over systemic injection with respect to cost considerations as well

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as patient compliance and comfort. One would have been motivated to do so because as taught by Mathowitz et al. ('313), oral administration of polymeric microspheres provide greater drug bioavailability via the mucosal membranes and offers advantages over systemic injection with respect to cost considerations as well as patient compliance and comfort. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by encapsulating sulindac in a polymeric microsphere and orally administering a combination of encapsulated sulindac and IL-22, one would achieve a method of providing a combination of encapsulated sulindac and IL-12 to a patient with greater bioavailability and patient compliance.

Therefore, NO claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF
5/30/2006


JEFFREY SIEW
SUPERVISORY PATENT EXAMINER